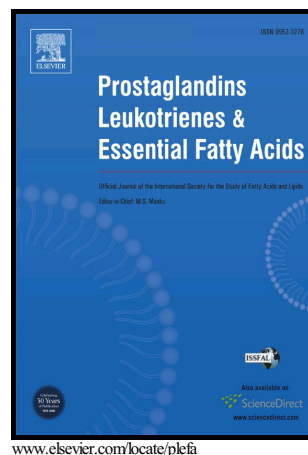


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M. Costabile, N.K. Bassal, J.P. Gerber, B.P. Hughes



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Inhibition of indoleamine 2,3-dioxygenase activity by fatty acids and prostaglandins: A structure function analysis.

Costabile M^{a,b,c*1}, Bassal NK^{a1}, Gerber, JP^a, Hughes BP^a.

^aUniversity of South Australia, School of Pharmacy and Medical Sciences, North Terrace, Adelaide, South Australia, 5000, Australia.

^bCentre for Cancer Biology, University of South Australia and SA Pathology, Frome Road, Adelaide, SA 5000, Australia;

^cSchool of Pharmacy and Medical Sciences, Division of Health Sciences, University of South Australia, Adelaide, SA 5001, Australia.

*Corresponding author. maurizio.costabile@unisa.edu.au.

Abstract

Indoleamine 2,3-dioxygenase-1 (IDO-1) catalyses the first and rate-limiting step in the metabolism of L-tryptophan. Degradation of L-Trp leads to the production of several immunosuppressive metabolites, including N-formyl kynurenine and kynurenine (Kyn). Apart from a normal physiological role, IDO-1 has also been identified to play a crucial role in immune suppression and tumour induced tolerance. Indeed, many primary tumours express high levels of IDO-1 compared to normal cells of the same stroma. IDO-1 is accepted as being an inducible negative regulator of T cell viability, proliferation and activation. As such, IDO-1 has become a target of intense interest for pharmacological inhibition, for the treatment of cancer. We have previously demonstrated that AA and the prostaglandin metabolite, PGD₂, repressed the IFN γ mediated activity of IDO-1 in THP-1 cells and human monocytes. In this study, we characterise the structure-function relationship of fatty acids and eicosanoids towards inhibition of IDO-1 activity in THP-1 cells and human monocytes. Using a commercial library of fatty acids, 55% of fatty acids inhibited IDO-1 activity. The

¹ Both authors contributed equally.

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